BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PTO # 2002-5057

USSR Patent
Document No. SU 1805392 A1

SPOSOB FORMIROVANIYA GRUPPY RISKA S ZABOLEVANIEM RAKA PISHCHEVODA

A.Z. Dovgaliuk, V.I. Stoliarov, and I.B. Semilutskaya

UNITED STATES PATENT AND TRADEMARK OFFICE
Washington, D.C.
October 2002

Translated by: Schreiber Translations, Inc.

Country	:	USSR
Document No.	:	SU 1805392 A1
Document Type	:	Patent Description
Language	:	Russian
Inventors	:	A.Z. Dovgaliuk, V.I. Stoliarov, and I.B. Semilutskaya
Applicants	:	Scientific Research Institute of Oncology named in honor of N.N. Petrov, Leningrad Institute of Medical Experts Upgrading and Scientific Research Institute of Hematology & Blood Transfusion
IPC	:	G 01 N 33/53
Application Date	:	April 25, 1989
Publication Date	:	March 30, 1993
Foreign Language Title	:	Sposob formirovaniya gruppy riska s zabolevaniem raka pishchevoda
English Title	:	A Method to Select the Esophagus Cancer Risk Groups

Union of Soviet Socialist Republics

(19) **SU** (11) **1805392 A**

(51)5 G 01 N 33/53

USSR State Patenting Authority
(USSR Gospatent)

PATENT DESCRIPTION

TO INVENTOR'S CERTIFICATE

---

(21) 4685572/14

(22) April 25, 1989

(46) March 30, 1993; Bulletin No. 12

(71) Scientific Research Institute of Oncology named in honor of N.N. Petrov, Leningrad Institute of Medical Experts Upgrading and Scientific Research Institute of Hematology & Blood Transfusion Scientific Research Institute of Physical & Chemical Medicine

(72) A.Z. Dovgaliuk, V.I. Stoliarov, and I.B. Semilutskaya

(56) Shabalin V.D and Serova L.D. Klinichskaya immunogematologiya (Clinical Immunohematology). Leningrad, "Meditsina" Publishers, 1988, p. 312

(54) **A METHOD TO SELECT THE ESOPHAGUS CANCER RISK GROUPS**

(57) **Abstract.** The invention concerns the field of medicine, specifically, oncoimmunology. The purpose of this invention is to improve the efficiency of selection of the risk groups of patients by detecting the HLA B35 antigens in the antigen composition of lymphocytes. The distribution patterns for the HLA antigen have been examined in the esophagus cancer patients. The antigen composition of lymphocytes has been examined with a standard lymphotoxic test and a panel of antiserums to the 23 antigens of HLA system. Lymphocytes for examinations were isolated by a defibrinated blood centrifugation method with the Ficoll/Verografin density gradient. The presence of the HLA B35 antigen in the antigen composition of lymphocytes forms the basis to form the risk groups of patients. 3 tables.

The invention concerns the field of medicine, specifically, oncology.

The purpose of this method is to improve the efficiency of selection of the risk groups of patients.

Distribution patterns for the HLA antigens have been examined in 109 esophagus cancer patients. As a reference group served data reported by L.D. Serova (1982) who had examined the distributions patterns of these antigens in 845 healthy individuals. The antigen composition of lymphocytes has been examined with a standard lymphotoxic test and a panel of antiserums to the 23 antigens of HLA system. Data on the specificity of lymphocytes effected by antiserums are shown in Table 1. Lymphocytes for examinations were isolated by a defibrinated blood centrifugation method with the Ficoll/Verografin density gradient. Blood samples for examinations were taken from the patients having cancers of esophagus confirmed by histology, X-ray and endoscopy examinations.

The group consisted of 109 esophagus cancer patients in total, including 92 male and 17 female patients aged from 40 to 75. Depending on localization of the process in esophagus

the distribution of patients was as follows: upper thoracic area - 12; intermediate thoracic area - 56; and lower thoracic area - 41 patient. Of the 109 patients total operative surgery was applied to 46 patients; the remaining 63 patients received symptomatic therapy. Follow-ups were completed for all the 109 patients.

Based on the comparative assessment of the reference HLA-antigen occurrence frequencies and those for the esophagus cancer patients (Table 1) we have found a statistically significant rise in the HLA B35 for our patients having cancer of esophagus (32 % as compared to 12.3 % in the reference group). Moreover, we noted a reduction in the occurrence frequency of HLA A19 (5.50 % as compared to 12.8 % in the reference group), B5 (6.4 % vs. 21.6 % in the reference), and B40 antigens (5.50 % as compared to 17.6 %) as compared to the reference group, which gives evidence for resistance of the individuals with these antigens to initiation of esophagus cancers.

As was noted above, our group of esophagus cancer patients consisted of 92 males and 17 females. Based on examination of HLA antigen distribution by sex (Table 1) is was found that the males showed statistically significant increase in

the HLA B35 antigen occurrence frequency (36.95 % as compared to 12.92 in the reference group) resulting in higher esophagus cancer incidence in males. They also showed reduction in occurrence frequencies of HLA A19 antigens (1.08 % as compared to 11.63 % in the reference), B5 (3.26 % as compared to 21.0 % in the reference), B12 (8.69 % as compared to 20.51 % in the reference), and B40 (5.43 % as compared to 11.95 % in the reference group). The group of females also showed a rise in occurrence frequencies of HLA B25 (23.52 % as compared to 10.61 % in the reference group) and reduction in the HLA A18 and B40 antigens (Table 1). It should be noted that female patients did not show any reduction in the B5 and B12 antigens: the parameters were the same as in the reference group.

Based on the distribution of the esophagus cancer patients by age it was found that in 14 cases they ranged from 40 to 49 in age; 50 patients were aged 50 to 59, and 35 patients were older than 60. Specifically, we emphasize that such a dangerous disease as cancer of esophagus have been never found in the patients younger than 40, and such pathologies were the most frequent for the patients older than 50 (85 patients). In our opinion just the patients older than 50

should be classified into the risk group, and this finding is valid both for males and females.

Experimental data on the distribution of HLA antigen by age of the patients are shown in Table 2. Our analytical consideration of occurrence frequencies for the HLA antigens vs. patients' age have revealed that the B35 antigen (Table 2) was the most frequent in all the age subgroups (28.57 % for patients younger than 49); 34 % for those less than 60, and 25.71 % for the patients older than 60. As to the A19, B5 and B40 antigens, it was noted that that the patients younger than 49 showed a statistically significant reduction in occurrence frequencies of B5, B12, and B40 antigens (See Table 2), which was not found at all in this age group [B40 - ? - Translator's Note]. The A19 antigen matched the standard. For the esophagus cancer patients classified into the largest group (patients aged 50 to 59; 50 cases) was observed a decrease in the occurrence frequencies of A19, B5, and B40 antigens (See Table 2) that govern resistance to the initiation of esophagus cancers, as compared to the reference group. The third age group of the patients (older than 60) showed a rise in the occurrence frequency for the B35 antigen (25.7 %); the parameter for A 19 and B5 was

reduced to 2.85 % and 5.71 %, respectively; no changes were noted for the B40 antigen.

Based on the detailed examination of the patient's anamneses and occupations it was found that in 26 cases (23.85 % of the total) our patients used to work in unhealthy conditions, specifically, as welders, solderers, jobs with application of alkali agents, chemically active substances, in the rubber industry, etc. Moreover, based on thorough examination of case histories it was found that 24 of our patients (22.01 %) had close relatives (mother, father, sister or brother) with different tumor diseases. The latter was found in 59 cases (54.12 % of patients).

Based on examination of distribution patterns of the HLA antigens in this group of patients (Table 3) it was found that this group was characteristic of the highest occurrence frequency of the HLA B35 antigen as compared to all groups studied based on anamneses and was equal to 42.37 % (as compared to 12.30 % in the reference standard), i.e. the presence of this antigen for patients older than 40 resulted in the highest risk of esophagus cancer incidence. As follows from the data shown in Table 3, for the group of patients with occupational hazards the HLA B35 antigen

reached 26.92 %, i.e. much higher than for the reference group (1.5 %). As the group of patients of unfavorable heredity, the HLA B35 antigen accounted for 3.33 % (as compared to 12.30 % in the reference group) (Table 3). On this basis it may be suggested that the esophagus cancer is a genetically determinated disease. The same as for the analyzed groups of patients we have observed decrease in the occurrence frequencies of HLA A19, B5, B8, B12 and B40 antigens, which govern resistance to the growth of the esophagus cancer.

Based on all the above, it may be argued that the patients older than 40 (specifically, males; females somewhat less frequently) of unfavorable heredity (close relatives had cancers) or those working in the occupational hazard environments should be classified into esophagus cancer risk group based on the presence of the HLA B35 antigen. Such a group requires special medical supervision to improve the statistics of early detection of esophagus cancers.

The presence of HLA A19, B5 and B40 antigens governs resistance to the development of esophagus cancers in humans.

Our method has been realized as follows:

Mr. V.N. Borovkov, the patient aged 54 was treated for cancer of the intermediate thoracic part of the esophagus (UI stage) in the clinic of the Scientific Research Institute of Oncology from September 16, 1985 to October 31, 1985 (Case History # 3142).

The patient at admission had complaints of pains in the half of his chest, dysphagia, difficulties in downward passage of high-residue food, weight loss (by 10 kg over 2 months).

Data from the anamnesis: the patient believes that he is a sick person within approximately two month, just after he noted discomfort at downward passage of high-residue food. He had the first appointment with his family doctor at his place of residence (Nevski District, City of Leningrad) in September, 1985. After X-ray examination he was diagnosed with cancer of the intermediate part of esophagus and referred to further examination and treatment to clinic of Scientific Research Institute of Oncology named in honor of Prof. N.N. Petrov (jurisdiction of the USSR Health Ministry). Furthermore, it was found that the patient is a high school graduate, and he works as a welder at a plant

for 15 years (i.e. occupational hazard). No unfavorable heredity found.

Unbiased examination data: The patient is in a moderately grave condition, skin covers clear; height - 180 cm; weight - 70.5 kg. Heart beats - 78/min; arterial pressure - 120/80 mmHg. Heart sounds attenuated, heart outlines within the allowable limits. Vesicular breathing above the lungs; no rales. The tongue is wet. The patient's belly shaped regularly, it takes part in breathing, soft at palpation, no pains; the patient's liver and spleen not enlarged. The lymphatic nodes, which are accessible for palpation are not enlarged.

Additional examinations:

Fibroesophagoscopy: detected ulcer-shaped tumor in the intermediate thoracic part of the esophagus, 4 cm in length. X-ray of the esophagus: X-ray examination has detected saucer-like cancer of the esophagus, 5 cm in length at the Th8-Th9 boundary of the indermediate/lower parts of the esophagus. Ultrasound examination of liver: no detected metastases. Within the pre-surgery period (from September 30, 1985 to October 02, 1985) the patient received a course of concentrated radiation therapy (gamma teletherapy), 499

sGy a dose, 1,497 sGy in total. Intrathoracic resection of the esophagus was completed with the Dobromislov-Torek method. Histology findings: nonkeratinizing squamous cell carcinoma of esophagus; the tumor penetrated all the layers of the esophagus wall; metastases at 3 paraesophagous lymph nodes. The post-surgery period without complications. Within the post-surgery period the patient's venous blood (10 ml) was sampled to examine the distribution pattern of blood antigens. Detected were the A2, A9, B15 and B35 HLA antigens. The patient was discharged from the hospital in a stable state to proceed with outpatient treatment.

Mr. A.I. Trofimov, the patient aged 64 stayed at the clinic of the Scientific Research Institute of Oncology named in honor of Prof. N.N. Petrov (jurisdiction of the USSR Health Ministry) for examinations from May 07, 1986 to May 26, 1986 due to cancer of the intermediate thoracic part of the esophagus, Stage IV.

The patient at admission had complaints of difficulties in downward passage of high-residue food, vomiting and food eructation, weight loss (by 15 kg over 5 months), weakness, indisposition.

Data from the anamnesis: the patient believes that he is a sick person from December 1985, just after he noted discomfort at downward passage of high-residue food and started to drink a lot of water to remove the difficulty. His dysphagia was getting more and more pronounced. He had the first appointment with a doctor in April, 1987 [a mistake - 1986 -? - Translator's Note]. After X-ray examination he was diagnosed with cancer of esophagus and referred to further examination and treatment to the clinic of Scientific Research Institute of Oncology named in honor of Prof. N.N. Petrov (jurisdiction of the USSR Health Ministry). The patient completed 4 grades of a primary school, and he is employed as an operator at the "Dinano" sports rowing club. Heredity unfavorable (patient's mother died from cancer of esophagus in 1950). No occupational hazards at the patient's working place.

Unbiased examination data: The patient is in a moderately grave condition, skin covers clear; heart beats - 78/min, rhythmic; arterial pressure - 130/80 mmHg. Heart sounds attenuated Vesicular breathing above the lungs, no rales. The tongue is wet; the patient's belly shaped regularly, it takes part in breathing, soft at palpation, no pains; the patient's liver and spleen not enlarged. The lymphatic

nodes, which are accessible for palpation not enlarged. Additional examinations:

Fibrogastroscopy: detected circular constriction of esophagus in the intermediate thoracic part of the esophagus. X-ray of the esophagus: X-ray examination has detected circular constriction of esophagus in the intermediate thoracic part of the esophagus, 7 cm in length.

Histology findings: squamous cell carcinoma of esophagus.

Within the period of patient's inpatient staying at the hospital, the esophageal obstruction became complete. Surgery of May 14, 1986: laparotomy, gastrostomy applied with the Witzel's method. During the operation metastases in the lymph nodes of lesser omentum were found and the patient was recognized to be inoperable. Within the post-surgery period the patient's venous blood was sampled to examine the distribution pattern of blood antigens. Laboratory examinations showed the distribution of A2, B12 and B35 HLA antigens. The patient was discharged from the hospital in a stable state to proceed with outpatient treatment.

Efficiency/Expected Efficiency. Application of our new method as compared to the existing ones has the advantages that:

-

- Our method contributes to the selection of esophagus cancer risk groups ;
- Improves early diagnostics of the cancer of esophagus
- Improves the remote consequences after treatment.

The Claim

A method to select the esophagus cancer risk groups based on examination of antigens of the HLA system in blood lymphocytes distinctive in that the presence of HLA B35 antigen in the antigen composition of lymphocytes is assessed to improve the accuracy of the method.

Table 1

The HLA antigen occurrence frequencies for esophagus cancer patients and healthy patients (distribution by sex)

HLA antigen	Healthy individuals n = 845	Esophagus cancer n = 109 (total)	Healthy males n = 619	Esophagus cancer (males) n = 92	Healthy females n = 226	Esophagus cancer (females) n = 27
HLA A - 1	19.76	29.35	19.54	30.43	20.35	23.52
A - 2	51.83	49.54	54.11	46.73	45.5	58.82
A - 3	26.98	30.27	26.49	30.43	28.31	29.41
A - 9	27.45	21.10	27.3	20.65	27.87	17.64
A - 10	19.64	19.26	19.87	20.65	19.02	17.64
A - 11	16.33	19.26	19.96	18.47	14.60	5.88
A - 19	12.78	5.50 +	11.63	1.08 +	15.92	0 +
A - 28	8.04	2.6	8.78	3.26	11.50	5.88
A - x	17.14	25.68	17.24	22.82	16.78	41.17
B - 5	21.65	6.42 +	21.0	3.26 +	23.45	23.52
B - 7	27.57	20.18	27.78	18.47	26.99	23.52
B - 8	14.91	17.42	15.5	17.39	13.27	17.64
B - 12	19.76	10.09	20.51	8.69	17.69	17.64
B - 13	6.86	8.25	6.3	8.69	8.40	5.88
B - 14	7.33	6.42	7.43	7.60	7.07	5.88
B - 15	11.73	8.25	11.14	7.60	13.27	5.88
B - 16	5.91	8.25	6.13	10.86	5.3	0 +
B - 17	7.57	8.25	5.97	9.78	11.94	0 +
B - 18	10.53	8.25	10.0	4.34	11.94	23.52

B - 21	3.55	2.75	3.39	4.34	3.98	0^{+}
B - 22	4.61	3.66	5.16	3.26	3.09	5.88
B - 27	9.94	7.33	11.14	6.52	6.63	11.76
B - 35	12.30	32.11 $^{+}$	12.92	36.95 $^{+}$	10.61	23.53 $^{+}$
B - 40	14.07	5.50 $^{+}$	11.95	5.43 $^{+}$	12.83	5.88 $^{+}$
B - 41	5.56	0 $^{+}$	5.81	3.86	4.86	0 $^{+}$
B - y	18.03	44.03	17.72	0 $^{+}$	18.51	29.42

Table 2

The HLA system antigen occurrence frequencies for esophagus cancer patients and healthy patients (distribution by age)

HLA antigen	Healthy individuals n = 845	Age of patients at initiation of esophagus cancer		
		From 40 to 49 n = 14	From 50 to 59 n = 50	From 60 to 70 n = 35
A - 1	19.76	14.28	26.6	45.71
A - 2	51.83	64.28	46.0	54.28
A - 3	26.96	42.85	32.0	17.14
A - 9	27.48	21.42	26.0	8.57
A - 10	19.64	7.1	18.0	25.71
A - 11	16.33	7.1	18.0	22.85
A - 19	12.78	14.28	6.0	2.85
A - 28	8.04	0	4.0	5.71
A - x	17.14	28.75	4.0	17.14
B - 5	21.65	7.142	6.0	5.71
B - 7	27.57	35.7	16.0	14.28
B - 8	14.91	21.42	22.0	14.28
B - 12	19.76	7.142	10.0	14.28
B - 13	6.86	21.42	8.0	5.71
B - 14	7.33	7.14	8.0	2.85
B - 15	11.73	0	8.0	14.28

B - 16	5.91	7.14	10.0	5.71
B - 17	7.57	0	14.0	5.71
B - 18	10.53	7.14	6.0	11.42
B - 21	3.55	0	0	11.42
B - 22	4.61	0	6.0	2.85
B - 27	9.94	7.14	8.0	8.57
B - 35	12.30	28.57	34.0	25.71
B - 40	14.07	-	6.6	14.28
B - 41	5.56	7.14	2.0	0
B	18.03	42.83	36.0	42.85

Table 2

The HLA system antigen occurrence frequencies for esophagus cancer patients and healthy patients (distribution by occupational hazards and unfavorable heredity)

HLA antigen	Healthy individuals n = 845	Occupational hazard + unfavorable heredity	Occupational hazard n = 26	Unfavorable heredity n = 24
1	2	3	4	5
A - 1	19.76	27.11	26.92	33.33
A - 2	51.83	52.54	46.15	45.83
A - 3	26.98	33.89	15.38	3.75
A - 9	27.45	15.25	19.23	33.33
A - 10	19.64	20.33	23.03	16.66
A - 11	16.33	13.55	19.23	16.66
A - 19	12.78	5.08	7.69	4.16
A - 28	8.04	5.08	3.84	-
A - x	17.14	25.42	38.46	1.25
B - 5	21.63	3.38	11.53	8.33
B - 7	27.57	19.64	15.38	16.66
B - 8	14.91	18.64	19.23	1.25
B - 12	19.76	11.86	3.84	1.25
B - 13	6.86	8.47	11.53	4.16

B - 14	7.33	6.77	7.69	4.16
B - 15	11.73	6.77	7.69	8.33
B - 16	5.91	5.08	15.38	4.16
B - 17	7.57	5.08	3.84	20.83
B - 18	10.53	5.08	3.84	16.66
B - 21	3.55	3.38	3.84	4.16
B - 22	4.61	3.38	3.84	4.16
B - 27	9.94	6.77	7.69	1.25
B - 35	12.30	42.37	26.92	33.33
B - 40	12.07	5.08	3.84	8.33
B - 41	5.56	3.38	-	-
B - y	18.03	45.16	-	29.16